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Position Paper

Human tissue research: EORTC recommendations on its practical consequences

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Abstract

Improvement in cancer care is possible by applying new treatment modalities, which are emerging from knowledge and discoveries coming from laboratory research. This is possible through international collaboration and the collection of tumour tissues. Creation of a European Organisation for Research and Treatment of Cancer (EORTC) Tumor Bank is a natural step in this direction, by offering tumour sample collection from patients entered in EORTC trials. The aim of such a bank is not only to improve the diagnostic review process, but also to facilitate translational research by allowing clinicians and basic scientists to enter into close collaborations. The EORTC Tissue Research Policy is developed to assure, under the EORTC legal framework, an ethical and scientific review of research projects, guarantee adequate information is given to patients, establish procedures on the use of materials, including legal aspects, and publication policies. Being part of the EU TubaFrost project, the EORTC will provide a common international platform for the use of tissues for research purposes, finding a balance between different laws and assuring scientific progress.

Keywords: EORTC; Tumor bank; Tissue research; Translational research

1. General introduction: laws governing tissue research

As large amounts of information on personal and clinical data can be extracted from tissue samples, it is important that the secondary use of tissue for research is governed by strict regulations to protect both the interests of the patient donating the tissue material and those of future patients.

Although there are broad principles regarding the use of human tissue material in Europe and the United States (US), the various laws and customs in the different countries or states show that national and state laws and customs still dominate [1]. Occasionally, there are conflicts in the laws and policies between these nations and states.

In the US, even though several states comply with the Common Rule of the Federal Law [2] (Federal Policy for the Protection of Human Subjects) which states that there has to be an Institutional Review Board (IRB) to review the scientific and ethical basis of proposed research projects and informed consents are to be obtained from patients, several states (for example, Washington, New Jersey and Illinois) have additional requirements for informed consent in research or treatment [1].

Some states also have restricted tissue testing and use, especially involving genetic testing and genetic information.

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To make matters worse, a new federal privacy rule (to be implemented in April 2003) could limit the use and release of patient data associated with tissue research if the data is not de-identified.

In Europe, the European law and regulations concerning the use and transfer of patient data associated with tissue samples is covered by the European Union (EU) Data Protection Directive [3]. This directive guarantees protection to patients concerning the processing and free movement of personal data.

An article [4] from the Convention on Human Rights and Biomedicine (Council of Europe) states that:

- patients should give their informed consent,
- research projects must be approved by an ethics committee or state authority,
- non-identifiable human biological material is subject to conditions,
- the transfer of material to another country is only possible if the recipient country has regulations with a similar level of protection as the sending country.

Although all member states implement the EU Data Protection Directive, some countries do have certain demands concerning tissue research. For example, in Sweden, the use of tissue research is very restricted [5] where patients donating the tissue will provide separate consent for each individual research protocol that will involve this patient's tissue material. On the other hand, in The Netherlands, research on anonymised human tissue material can be performed, unless the person from which the tissue originated from raised an objection to research (opt-out system) [6,7]. Recently, a code of conduct for the banking and use of human tissue has been proposed in The Netherlands and guidelines have also been provided in the United Kingdom (UK) by the Medical Research Council and Department of Health [8].

Proper collaboration between researchers within Europe and between Europe and the US will only be possible if there is harmonisation of the rules (for informed consent, tissue and data release and use etc.) at the national or European levels.

2. EORTC Tumor Bank

Translational research is one of the activities that EORTC groups are performing. Through EORTC clinical trials, tissue material collected from patients is sent to laboratories around Europe where it is used for research. Intergroup clinical trials with the US also mean that there is a requirement for material and data to be exchanged on a more international level.

In order to support translational research and tumour banking within the context of EORTC clinical trials, the EORTC Pathology group and EORTC Data Center designed and set up the EORTC Tumor Bank in September 2000. The main aims of this EORTC Tumor Bank are to:

1. Improve and harmonise histological review (especially between the local and review pathologists) in EORTC clinical trials, by providing dedicated logistical support for the collection and storage of paraffin blocks, glass slides, pathology forms and digital images representative of the tumour.
2. Support translational research, in the context of EORTC clinical trials, by providing rapid access to information (via the Virtual Tumor Bank (VTB) website) and tumour tissues needed for research projects. This information will include details about material stored centrally in the EORTC Tumor Bank Office in Brussels and material stored locally (such as frozen tumour tissue) within hospital pathology laboratories across Europe.

This document has been prepared in order to provide information to investigators and scientists involved in EORTC clinical trials connected with the EORTC Tumor Bank. The aim of this policy is to document the general principles involved in EORTC Tissue Research performed during the progress of the clinical trial (prospective) and research carried out after the clinical trial has closed (retrospective). The second section of the document describes the EORTC Tumor Bank.

It also provides information on the:

- rules of ethical and scientific review of proposed research projects by the EORTC Translational Advisory Committee and the EORTC Institutional Review Board;
- intellectual property rights acquired during EORTC Tissue research and Patient Information Sheet-Informed Consent;
- rules on use of material in translational research by EORTC groups, academic institutes/organisations and pharmaceutical industries;
- publication policies;
- contracts and legal documents to deal with issues on the use of materials, and results of the tissue research such as benefits, patenting and possible drug registration.

As an extension of the initial EORTC Tumor project initiated in 2000, the EORTC Data Center participates in a larger project supported by a grant from the European Commission to create a Pan-European Tumor bank: the 'TuBaFrost' project.

The objective of this project is to develop an European human frozen tumour tissue bank by creating a network of collections of well-documented, standardised frozen

tumour samples (with their corresponding accurate diagnoses) for research. These samples are stored in major cancer centres and universities throughout Europe. The information on these locally stored, frozen tumour samples is contained in the central EORTC Virtual Tumor Bank which can be accessed via the Internet, together with rules for access and the use of tissues complete with a European code of conduct to comply with various legal and ethical regulations in European countries [9,10].

2.1. General principles for EORTC tissue research

The EORTC has a longstanding tradition and experience in conducting clinical trials in Europe and beyond. However, improvements in cancer care are possible not only by running trials with new treatment modalities, but also through performing basic science research.

Translational research can be defined as 'research exploiting the insights gained in fundamental biomedical research for the benefit of patients with cancer. Examples of translational research and how they have been applied to cancer treatments include:

- Identification of specific aberrations through chromosomal and genetic analyses of tumours leading to diagnostic, predictive and prognostic procedures.
- Identification of substances that can be used as drugs in anti-angiogenic therapy.
- Studies into various biological markers expressed on tumour cell membrane surfaces leading to the development of drugs that can be targeted against these tumour markers. These biological markers or tumour biomarkers can also be used in screening, diagnosis, as prognostic indicators, to monitor therapy, and/or for the early diagnosis of relapse for many cancers for example prostate-specific antigen (PSA) in prostate cancers.

These types of translational research are possible through the collection of tumour tissue from patients entered into cancer clinical trials. Tumour banks are developed to facilitate the collection, storage and distribution of tumour tissue samples for translational research projects. In addition, the application of advances in information technology, for example telemedicine, has enabled efficient management and accessibility to these stored samples.

Creative proposals for translational studies should emerge in EORTC groups from stimulating multidisciplinary collaborations between clinicians, pathologists and basic scientists. The role of the pathologist in translational research is two-fold: to promote an active role for pathologists with a proper background in the research of the EORTC groups (in co-operation with scientists from other groups), and to make (tumour) material accessible for research. Pathologists from institutions where material originates will be actively involved in the process of material release for a specific translational research project.

Translation of recent advances in understanding the molecular and cellular pathology of cancer into a benefit for patients is one of the activities of the EORTC groups. Translational research is possible through the collection of tumour tissue from patients entered in EORTC trials.

Tumour sample collection and tissue research can be done prospectively, following the clinical trial, or, retrospectively, after the clinical trial has been closed.

Pharmaceutical companies or even non-EORTC groups can be involved as partners in tissue research, depending on the trial and translational research project.

However, regardless of how and where tissue collection is performed and laboratory analysis done, general principles have been developed and set as a EORTC Tissue Research Policy. These have been approved by the EORTC Board and are now being applied. This is to ensure that scientific and ethical principles under the EORTC legal framework are respected for all types of research that is conducted.

Therefore:

- in cases of prospective material collection (new trials beginning after the initiation of this policy), patients must be adequately informed about the translational research project.
- in cases where material has already been collected, but there is no consent for the secondary use of material (future research), reasonable efforts should be made to recontact the patient. If this is not possible (e.g. the patient has died or is lost to follow-up), research projects on this material might, however, still be allowed by the EORTC, under certain circumstances and conditions (in certain countries, some national regulations foresee exceptions for the use of stored tissue) if the project has successively gone through an ethical and scientific review process.
- ethical and scientific review is mandatory before any material can be made available for research (submission to EORTC TRAC and EORTC IRB).
- once EORTC TRAC and IRB have reviewed the project, it should be submitted, for review, to the institutional IRB/Ethics Committees from which the project originates. In cases where no such Ethics Committee exists, the project will be submitted to one or two external IRB at institutions from which material was collected.
- any intellectual property rights acquired by using

tissue samples of patients entered in the EORTC clinical trials should lead to compensation to EORTC.
- publication rules according to EORTC policy must be respected.

2.2. Histological review

Patients are included in EORTC clinical trials on the basis of a (local) pathological diagnosis.

Final pathological diagnosis is based on the review done by the pathologist experienced in the specific disease. This is not only for quality assurance purposes, but also to assure the level of confidence in the pathology diagnosis.

2.3. Purpose of the EORTC Tumor Bank

The Tumor Bank has been set up to improve and harmonise the histological review in EORTC clinical trials by providing dedicated logistical support in the collection and storage of paraffin block/slides(s), pathology forms and digital images.

The Tumor Bank will also support translational research in the context of EORTC trials, by providing rapid access to information (via VTB Website) and tumour tissues needed for side-studies.

In 2002, the EORTC Data Center also received a grant from the European Commission to participate in the 'TuBaFrost' project (2002–2005). The objective of the TuBaFrost project is to create a network of collections of well-documented, standardised frozen tumour samples for research stored in cancer centres and university hospitals across Europe.

The initial costs related to supporting the creation of the EORTC Tumor Bank came from the Parthenon Trust (2000–2003), the costs related to the new TuBaFrost project are partially covered by the European Commission Grant.

2.3.1. Definitions

Translational research—Integrated clinical-laboratory investigations designed to improve the prevention, diagnosis and/or treatment of cancer. Involves both clinical and laboratory investigations, or laboratory investigations on clinical material collected during clinical trials.

Real tumor bank—EORTC Tumor Bank Office, which is located at the EORTC Data Center in Brussels. Glass slides and paraffin blocks, related to EORTC trials, will be collected and stored here.

Virtual Tumor Bank (VTB)—images and information about the patients and material are stored in VISTA (EORTC Clinical database) and the VTB database.

Pathology review — This is review of the local diagnosis by a single central pathologist and/or a panel of pathologists.

Translational researcher—A scientist or clinician who is involved in a laboratory and/or clinical research project and is interested in obtaining some material collected in an EORTC clinical trial(s).

Digitisation—Creating digitised images from the glass slides (e.g. using a digital camera mounted on a microscope).

2.3.2. Objectives of the EORTC Tumor Bank

The EORTC Pathology Group and the EORTC Data Center started the Tumor Bank in September 2000. This was initially set up as a 3-year pilot project, with a future perspective to serve the whole of the EORTC.

The aims of the Tumor Bank are to:

1. Improve and harmonise the histological review in EORTC clinical trials (using telepathology).

   Fig. 1 shows how the flow of material (slides/paraffin blocks), forms and images is carried out in the review process of EORTC trials supported by the EORTC Tumor Bank.

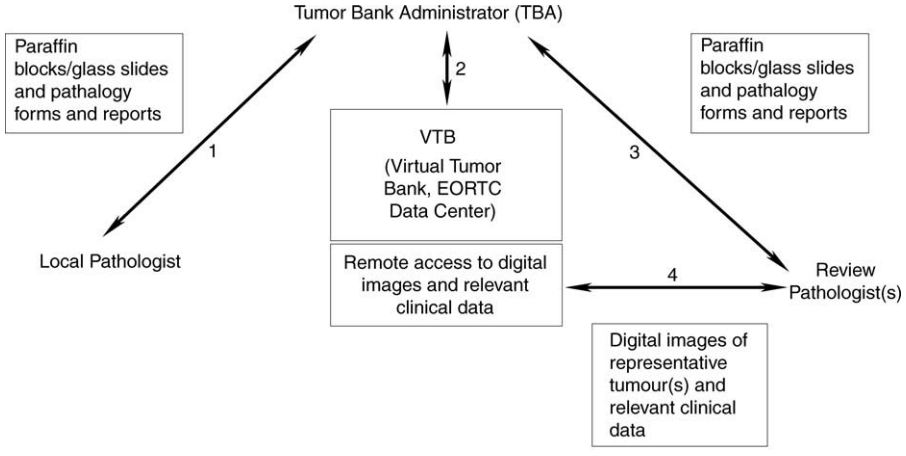

Fig. 1.

2. Facilitate the translational research in the context of EORTC trials, by providing rapid access to the tumour tissues needed for side-studies (using an online search engine).

Fig. 2 illustrates the communication and flow of information and material between the entities involved in translational research involving the EORTC Tumor Bank.

Details on the rules and process involved in the above diagram are explained in further detail in Section 2.3.4.2.

For these aims to be accomplished, the following activities will take place:

- collection and centralised storage of paraffin blocks/slides (real tumour bank)
- collection of pathology forms (virtual tumour bank)
- collection of material-related information (decentralised collection of paraffin blocks, glass slides and frozen material) (virtual tumour bank).
- collection (online) of digital images (virtual tumour bank).
- Development of an online VTB website where pathologists and researchers can:

1. access the information on local and review diagnoses, site of disease, etc.
2. access the material information (staining, tumour type, fixation, current location, etc.)
3. access the digital images (overview (low magnification) and representative (high magnification))
4. facility for pathologists (involved in specific trials) to upload digital images and diagnoses online into the patient's case notes.

Experience coming from the pilot phase will serve as a basis for full implementation in EORTC trials as a whole.

2.3.3. Responsibilities

- EORTC Tumor Bank Executive Committee (ETBEC)

The EORTC Tumor Bank is managed by the ETBEC. This committee is composed of members of the EORTC Data Center and the EORTC Pathology group:

- EORTC Tumor Bank Administrator (TBA)
- EORTC Tumor Bank Coordinator
- Chair of the EORTC Pathology group
- Chair of the EORTC Tumor Bank
- Chair of the Telematics subcommittee of the EORTC Pathology Group

The committee meets monthly in a teleconference to discuss the progress of the pilot phase and the next necessary actions to take in its development.

- External support to the Tumor Bank Project
- EORTC Executive Committee
- EORTC Protocol Review Committee (PRC)
- EORTC Translational Research Advisory Committee (TRAC)
- EORTC Institutional Review Board (IRB)
- Chairman of the EORTC Laboratory Research Division
- Representatives of the EORTC IT unit
- EORTC Data Center Legal Advisor

2.3.4. Use of materials

2.3.4.1. For review/diagnostic purposes. As the patients are randomised into clinical studies, a request will be made from the EORTC Tumor Bank Office to the local pathologist to send the material (paraffin blocks/glass slides), completed local pathology form and institutional pathology report to the EORTC Tumor Bank Office in Brussels.

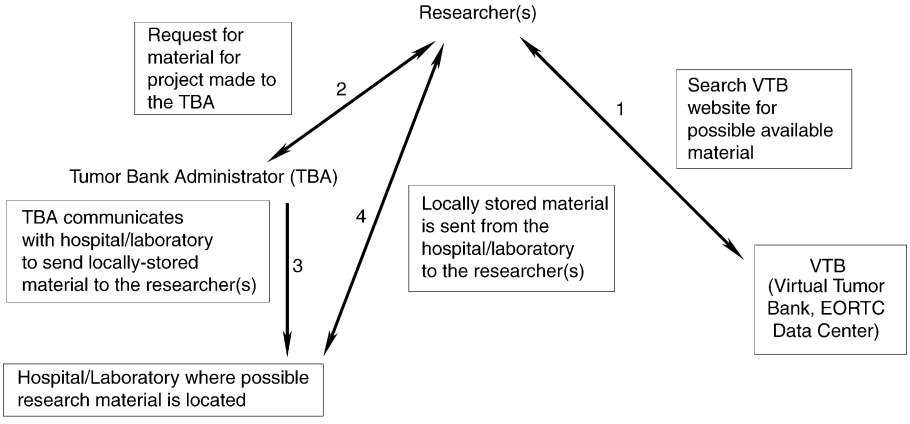

Fig. 2.

These forms and material are then relayed to the review/reference pathologist of the study.

If a panel review is to take place within the study, the EORTC Tumor Bank Office will contact the members and instruct them to use the VTB website to review into the patient case and images and submit their diagnoses.

Material (paraffin blocks/glass slides) will be permanently stored in the EORTC Tumor Bank Office unless the local pathologist has specifically requested return of some or all of the material. In the latter situation, all the material requested will be sent back to the local pathologist.

As soon as the pathology review has been completed for each patient case, the EORTC Tumor Bank Office will distribute, to all the pathologists involved in reviewing of the patient, a copy of all the review pathology forms.

2.3.4.2. For translational research.

• *Prospective collection of samples*: The description of translational research and type of material required for translational research for the study will be found in the PRC/TRAC-approved protocol. The EORTC Tumor Bank Office will send the material (paraffin blocks/slides) required for the study's translational research to the laboratory performing translational research.. For distribution of frozen material (this is never stored in the EORTC Tumor Bank Office), this will be evaluated and discussed on a case-by-case basis between the EORTC TB Office and the Group, taking into account the financial status, logistical organisation, and time frames.

It will be the responsibility of the EORTC Tumor Bank Office to retrieve any unused material from the laboratory performing the translational research.

• *Retrospective studies on samples previously collected*

○ *EORTC Group/single EORTC institute requesting material from its own trial*: The responsible scientist (as mentioned in the protocol) will send the full project with a list of material required to the EORTC Tumor Bank Office. The EORTC Tumor Bank Office will then forward this to the ETBEC, TRAC and the EORTC IRB.

TRAC has an advisory role especially related to scientific matters. IRB is involved in approving the ethical aspects and will make the final approval of the project.

After approval, the EORTC Tumor Bank Office will send the material (in cases of paraffin blocks/slides stored in the EORTC Tumor Bank Office) or will contact the relevant institution where the respective material (locally stored, paraffin blocks/glass slides and frozen tissue) is stored. The latter will then be sent directly to the laboratory responsible for the translational research of the trial. The TBA will receive a copy of the material form that is sent and returned with the locally stored material.

In case there is disagreement in approving the project and use of material, the EORTC Executive Committee will mediate the discussion between TRAC, IRB and the responsible scientist.

○ *EORTC Group/single EORTC institute requesting material from another EORTC Group*: The responsible scientist (as mentioned in the protocol) will send the full project with a list of material required to the EORTC Tumor Bank Office. The EORTC Tumor Bank Office will then forward this to the ETBEC, the TRAC, EORTC IRB and the chairman of the group where the material originated. The chairman(s) of the group(s) must approve the release of material.

TRAC has an advisory role especially related to scientific matters. IRB is involved in approving the ethical aspects and will make the final approval of the project.

After approval, the EORTC Tumor Bank Office will send the material (in cases of paraffin blocks/slides stored in the EORTC Tumor Bank Office) or will contact the relevant institution where the respective material (locally stored, paraffin blocks/glass slides and frozen tissue) is stored. The latter will then be sent directly to the laboratory responsible for the translational research of the trial. The TBA will receive a copy of the material form that is sent and returned with the locally stored material.

In case there is disagreement in approving the project and use of material, the EORTC Executive Committee will mediate the discussion between TRAC, IRB, chairman(s) of the group(s) and the responsible scientist.

○ *Request from Academic Institute/Organisations outside the framework of EORTC* Academic institutes/organisations could request access to tissue samples for their research work. In these situations, they could take the opportunity of using tissue samples from the EORTC Tumor Bank following approved agreement/contract described under Section 2.3.4.4.

The responsible scientist (as mentioned in the project) will send the full project to the EORTC Tumor Bank Office. The EORTC Tumor Bank Office will then forward this to the ETBEC, the TRAC, the EORTC IRB and the chairman of the group where the material originated. The chairman(s) of the group(s) must approve release of material.

TRAC has an advisory role especially related to scientific matters. IRB is involved in approving the ethical aspects and will make the final approval of the project.

After approval, the EORTC Tumor Bank Office will send the material (in cases of paraffin blocks/slides stored in the EORTC Tumor Bank Office) or will contact the relevant institution where the respective material (locally stored, paraffin blocks/glass slides and frozen tissue) is stored. The latter will then be sent

directly to the laboratory responsible for the translational research of the trial. The TBA will receive a copy of the material form that is sent and returned with the locally stored material.

In case there is disagreement in approving the project and use of material, the EORTC Executive Committee will mediate discussion between TRAC, IRB, chairman(s) of the group(s) and the responsible scientist.

○ *Request from the pharmaceutical industry*

Pharmaceutical companies may wish to perform tissue research to support their drug development and registration process within the framework of cooperation with EORTC.

The responsible scientist (as mentioned in the project) will send the full project to the EORTC Tumor Bank Office. The EORTC Tumor Bank Office will then forward this to the ETBEC, the TRAC, the EORTC IRB and the chairman of the group where the material originated. The chairman(s) of the group(s) must approve release of material.

TRAC has an advisory role especially related to scientific matters. IRB is involved in approving the ethical aspects and will make the final approval of the project.

After approval, the EORTC Tumor Bank Office will send the material (in cases of paraffin blocks/slides stored in the EORTC Tumor Bank Office) or will contact the relevant institution where the respective material (locally stored, paraffin blocks/glass slides and frozen tissue) is stored. The latter will then be sent directly to the laboratory responsible for the translational research of the trial. The TBA will receive a copy of the material form that is sent and returned with the locally stored material.

In case there is disagreement in approving the project and use of material, the EORTC Executive Committee will mediate discussion between TRAC, IRB, chairman(s) of the group(s) and the responsible scientist.

2.3.4.3. Publication policy for results of side-studies related to translational research

Results of side-studies related to translational research may be published or presented to the medical community before trial maturity and publication of the primary endpoint (final results) of the trial, provided the data related to those side-studies are mature and provided there is no direct relationship between these results and the primary trial endpoint.

Such publications must be reviewed, authorised and approved by the statistician and coordinating physicians in charge of the trial, chairman of group and study coordinator of the trial (along which material has been collected).

A list of authors must be created at start of project/side-study so that unnecessary conflicts do not occur.

The EORTC group(s) concerned by the data transfer will be clearly acknowledged and the EORTC trials will be referenced with their official number and title.

Inclusion of the pathologists (who provided respective material for research) and EORTC Data Center representative(s) as co-authors will be considered for each project on a case-by-case basis with respect to the extent of their involvement in the project.

2.3.4.4. Contracts and legal documents

For all types of translational research, a contract must be created for each project whether it is between academic laboratories or pharmaceutical companies.

This contract will address specific conditions for use of material and results coming from this research (benefits, patenting and any possible drug registration).

This contract will guarantee appropriate compensation for EORTC research for any intellectual property rights acquired. Any intellectual property rights must be discussed with the EORTC Executive Committee on a case-by-case basis.

2.3.5. Patient information sheet—informed consent (PIS-IC)

Patients must receive complete and adequate information regarding the translational research project (aims, storage, data protection, voluntary aspects, approval system, etc.). This is mandatory in order to comply with the high ethical standards that are part of the scope of EORTC clinical trials (i.e. the Helsinki Declaration, ICH GCP, national laws and, in the future, the European Directive on clinical trials). Therefore, the EORTC foresees standard PIS templates as follows:

- in cases of a translational research project, which is an optional part of a prospective clinical trial, the patient will provide consent for the clinical trial, as well as filling in a separate consent form allowing the translational research to be done using their tissue (biological material).
- in cases of a translational research project, which is a mandatory part of a prospective clinical trial, the patient will provide consent for both the clinical trial and translational research on their tissue (biological material).

In cases where the material has already been collected locally, but there is no consent for the secondary use of the material (future research), reasonable efforts should be made to recontact the patient. If this is not possible (e.g. the patient has died or been lost to follow-up), research projects on this material might, however, still be allowed by the EORTC, under certain circumstances and conditions (in certain countries, some national reg-

ulations foresee exceptions for the use of stored tissue) if the project has successively gone through an ethical and scientific review process.

It cannot be excluded that results from the use of patient's biological material could lead to an acquisition of intellectual property rights by the EORTC. Patients will not receive any financial return. Should there be any financial return for the EORTC, it will be re-invested only in cancer research to improve future cancer care.

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